Remarks

Claims 14, 16, and 19-95 are pending in the instant application. Claims 34 and 37 have been amended. Claim 34 has been amended to further clarify the relationship between the recited structural elements in the claim. Claim 37 has been amended to further clarify the term "protein" in step (b) of the claim. No new matter has been added.

Applicants thank the Examiner for acknowledging the timely traversal of the restriction requirement. Applicants bring to the Examiner's attention that they have petitioned the final restriction requirement (Paper No.17) under 37 C.F.R. §§ 1.144 and 1.181(c).

I. Drawings

Applicants thank the Examiner for indicating that the drawings submitted on December 8, 1999 are approved.

II. Response to Amendment

Applicants thank the Examiner for indicating that the Declaration under 37 C.F.R. § 1.132 filed December 8, 1999 was sufficient. *See,* Paper No.17, page 3, third paragraph.

III. Double Patenting

The Examiner has indicated that claims 21, 26, 33, and 35-37 have been rejected under the judicially-created doctrine of obviousness-type double patenting as allegedly being unpatentable over claim 32 of U.S. Patent No. 5,981,215. *See,* Paper No.17, page 3, last paragraph.

Applicants respectfully disagree, but solely in the interest of facilitating prosecution, Applicants have submitted a Terminal Disclaimer, as it applies to claims 21, 26, 33, and 35-37, thereby obviating the rejection. Accordingly, Applicants respectfully request that the obviousness-type double patenting rejection of claims 21, 26, 33, and 35-37 be withdrawn.

IV. Claim Objections

The Examiner has objected to claims 21, 33, and 35-37 as allegedly encompassing multiple patentably distinct inventions. *See* Paper No. 17, page 4, second paragraph. As stated

above, Applicants have petitioned the final restriction requirement under 37 C.F.R. §§ 1.144 and 1.181(c), therefore, until the petition is acted upon, Applicants will not amend or cancel these claims.

V. Utility Rejections Under 35 U.S.C. § 101

The Examiner has rejected claims 21, 26, 33, and 35-37 under 35 U.S.C. § 101 because the claimed invention is allegedly not supported by either a substantial and specific utility or a well-established utility. In particular, the Examiner states:

> [t]he utility set forth in the specification p.17, last paragraph, is that of pancreatic cancer diagnosis. This is based on 'An initial Northern blot analysis [that] has shown very high expression in pancreatic cancer cells.' For several reasons this is not a specific or substantial utility. First, it is not known how the level of expression compares to expression in normal noncancerous cells, nor if the expression was analyzed in cell cultures or in cancerous tissue. Markers for cell lines are not necessarily representative of primary cell cultures or tissue since it is well known that cells can undergo changes in expression when cultured for extended passages. Also, a cancer cell line is representative of only a single sample (cell lines originate from 1 patient's cells), which is not enough information to conclude that protein alteration in that cell line is a universal phenomenon in all or most pancreatic cell samples. Second, polynucleotide expression is not necessarily indicative of protein expression. There is no information on altered level of protein (the claimed product) in pancreatic cancer cells.

Applicants respectfully disagree and traverse.

Preliminarily, Applicants respectfully assert that the Examiner has not met the burden that is necessary to establish and maintain a rejection for lack of utility under 35 U.S.C. § 101. According to M.P.E.P. § 2107, the burden is on the Examiner to establish that it is more likely than not that a person of ordinary skill in the art would not consider the utility asserted by Applicants to be specific, substantial, and credible. *See* M.P.E.P. § 2107 at 2100-30 (emphasis added). In addition, the Federal Circuit has recently stated with respect to the rejection of claims for lack of utility that:

> The PTO cannot make this type of rejection...unless it has reason to doubt the objective truth of the statements contained in the written description. *See In re Brana*, 51 F.3d at 1566, 34 U.S.P.Q.2d at 1441 ('[T]he PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does

> the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility.') (citations omitted); *In re Marzocchi*, 439 F.2d 220, 223, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971)....The PTO may establish a reason to doubt an invention's asserted utility when the written description 'suggest[s] an inherently unbelievable undertaking or involve[s] implausible scientific principles.' *In re Brana*, 51 F.3d at 1566, 34 U.S.P.Q.2d at 1441; see also *In re Eltgroth*, 419 F.2d 918, 164 U.S.P.Q. 221 (C.C.P.A. 1970) (control of aging process). *In re Cortright,* 49 U.S.P.Q.2d 1464, 1466 (Fed. Cir. 1999).

For the reasons set forth below, the Examiner has not met the burden that is necessary to establish and maintain a rejection for lack of utility under 35 U.S.C. § 101.

In order to find that an asserted utility is not specific or substantial, the burden is on the Examiner to make a *prima facie* showing that it is more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the Applicant to be specific or substantial. *See*, M.P.E.P. § 2107.02(IV); Utility Examination Guidelines at 1098, col. 3 (emphasis added). Such a *prima facie* showing must contain (1) an explanation that clearly sets forth the reasoning used in concluding that the asserted utility for the claimed invention is not both specific and substantial nor well-established; (2) support for factual finding relied upon in reading this conclusion; and (3) evaluation of all relevant evidence of record, including utilities taught in the closest prior art. *See id.* In the instant case, the Examiner has simply provided generalized statements that "markers for cell lines are not necessarily representative of primary cell cultures or tissue" and that "polynucleotide expression is not necessarily indicative of protein expression." (emphasis added). *See*, Paper No.17, page 4, last paragraph. These statements do not amount to a *prima facie* showing that it is more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the Applicant to be specific or substantial.

Notwithstanding the above discussion, Applicants contend that, contrary to the Examiner's allegations, Applicants have set forth in the specification statements that clearly provide the specific and substantial asserted utilities that the Examiner alleges is lacking. For example, the instant application discloses, for example, at page 2, lines 10-16; page 4, lines 6-8 and 22-24; and Figure 2, that polypeptides corresponding to SEQ ID NO: 2, as well as those encoded by the cDNA contained in ATCC Deposit No. 97142, have amino acid sequence homology to cripto growth factor, a known tumor marker which is upregulated in cancer

tissue, e.g., pancreatic cancer tissue. The specification also teaches at page 4, lines 29-30, that Northern blot analysis has shown very high expression of the criptin growth factor of the invention (CGF) in pancreatic cancer cells. Moreover, the specification discloses at page 2, lines 7-9 and page 17, lines 32-34, that CGF is overexpressed and secreted by cancer cells, e.g., pancreatic cancer cells. Additionally, the specification discloses, for example, at page 3, line 7-9; and page 27, line 18 to page 28, line 17, that antibodies may be generated against CGF polypeptides of the invention. Furthermore, Applicants have asserted that CGF polypeptides of the invention are useful, for example, as a diagnostic of pancreatic cancer. *See,* specification at page 17, line 32 to page 18, line 17.

Contrary to statements made by the Examiner, Applicants submit that the above-asserted utilities for the CGF polypeptides of the invention are specific and substantial. M.P.E.P § 2107(II) states (emphasis added):

> If the applicant has asserted that the claimed invention is useful for any practical purpose (i.e., it has a 'specific and substantial utility') and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.... An applicant need only provide one credible assertion of specific and substantial utility for each claimed invention to satisfy the utility requirement. M.P.E.P § 2107(II) at 2100-29.

Moreover, M.P.E.P. § 2107.01(I) states:

> [o]ffice personnel should distinguish between situations where an applicant has disclosed a specific use for or application of the invention and situations where the applicant merely indicates that the invention may prove useful without identifying with specificity why it is considered useful. For example, indicating that a compound may be useful in treating unspecified disorders, or that a compound has 'useful biological' properties, would not be sufficient to define a specific utility for a compound.... A general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent disclosure of what condition can be diagnosed. Contrast the situation where an applicant discloses a specific biological activity and reasonably correlates that activity to a disease condition. Assertions falling within the latter category are sufficient to identify a specific utility for the invention. Assertions that fall in the former category are insufficient to define a specific utility for the invention... M.P.E.P. § 2107.01(I) at 2100-32.

Applicants have clearly disclosed in the specification that CGF polypeptides of the invention are useful, for example, as a diagnostic of a specific disease, i.e., pancreatic cancer. The

Examiner makes note of this assertion at page 4, last paragraph of the Office Action (Paper No.17). In addition, Applicants have disclosed that increased expression of the CGF polypeptides correlates to a specific disease, e.g., pancreatic cancer. More specifically, the specification discloses that CGF is highly expressed in pancreatic cancer tissue and "an excessive amount of CGF protein allows a pancreatic cancer diagnosis." *See,* e.g., specification at page 17, line 32 to page 18, line 17; and page 4, lines 29-30. Therefore, in accordance with M.P.E.P. § 2107, Applicants have asserted that the claimed invention is useful for a specific practical purpose.

Moreover, Applicants submit that the above-asserted utilities for the CGF polypeptides of the invention are substantial. M.P.E.P. § 2107.01(I) states (emphasis added):

> [a] substantial utility defines a real world use.... An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a 'real world' use in identifying potential candidates for preventive measures or further monitoring...any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial utility.' M.P.E.P. § 2107.01(I) at 2100-32.

Applicants submit that diagnosis of pancreatic cancer is a "real world" use, which clearly provides a public benefit. In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 21, 26, 33, and 35-37 under 35 U.S.C. § 101.

Even though the Examiner has not discussed credibility of the asserted utilities, Applicants submit that the above discussed utilities would be credible to one skilled in the art in light of the disclosure presented in the instant specification, as well as what was known in the art at the time of the earliest priority date of the invention. As mentioned above, the specification discloses that the polypeptide of SEQ ID NO:2 is homologous to a known tumor marker (i.e., cripto growth factor), the CGF of the invention is highly expressed in pancreatic cancer tissue, and that "an excessive amount of CGF protein allows a pancreatic cancer diagnosis." *See,* e.g., specification at page 17, line 32 to page 18, line 17; page 4, lines 29-30; page 2, lines 10-16; page 4, lines 6-8 and 22-24; and Figure 2. In addition, Applicants submit PCT publication WO 01/77322 (Exhibit A), which discloses a cryptic-like secreted protein that is 99.5% identical to the CGF polypeptide of SEQ ID NO:2. This publication also

discloses that the cryptic-like secreted protein is expressed in tumors of the pancreas and that the protein could "function as a tumor marker and as a drug target to specifically target cryptic-like expressing tumor cells." *See,* Exhibit A at page 3, lines 18-24. This reference clearly supports the Applicants' original assertion that the CGF protein of the invention is useful, for example, as a diagnostic of pancreatic cancer. Therefore, even though the Examiner has not explicitly discussed credibility, Applicants submit that the above-discussed utilities would be credible to one skilled in the art based on the totality of the evidence and reasoning provided.

Moreover, Applicants respectfully point out that they do not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty or provide actual evidence of success in treating humans where such a utility is asserted. As stated in the M.P.E.P. § 2107.03 (I) at 2100-34 (emphasis in original), "[c]ourts have repeatedly found that the mere identification of a pharmacological activity of a compound that is relevant to an asserted pharmacological use provides 'an immediate benefit' and thus satisfies that utility requirement." All that is required of Applicants is that there be a *reasonable* correlation between the biological activity and the asserted utility. *See Nelson v. Bowler*, 626 F.2d 853, 857 (C.C.P.A. 1980). Applicants submit that activity of CGF disclosed in the specification and discussed above is reasonably correlated with the asserted diagnostic use of the claimed polypeptides.

As mentioned above, the Examiner has not met the burden that is necessary to establish and maintain a rejection for lack of utility under 35 U.S.C. § 101. Even assuming *arguendo* that the Examiner has made a *prima facie* rejection for lack of utility, Applicants have successfully rebutted the rejection with evidence and reasoning supporting Applicants' asserted utilities. Applicants assert that one of ordinary skill in the art would certainly consider Applicants' asserted utility of the invention to be *specific, substantial, and credible* and clearly would have no basis for considering these asserted utilities to be "false." "When a properly claimed invention meets at least one stated objective, utility under 35 U.S.C. §101 is clearly shown." *Raytheon v. Roper*, 724 F.2d 951, 958 (Fed. Cir. 1983). Accordingly, Applicants respectfully request that the rejection of pending claims 21, 26, 33, and 35-37 under 35 U.S.C. § 101 be reconsidered and withdrawn.

VI. Rejection Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 21, 26, 33, and 35-37 under 35 U.S.C. § 112, first paragraph for alleged lack of enablement. *See,* Paper No. 17, page 5, second and third paragraph. In particular, the Examiner states that since the claimed invention is allegedly not supported by either a specific or substantial or well-established utility, one skilled in the art would not know how to use the claimed invention. *See*, Paper 17, page 5, third paragraph.

For the reasons discussed above in response to the rejection under 35 U.S.C. § 101, the claimed invention is supported by a credible, specific, and substantial utility. The Examiner "should not impose a 35 U.S.C. § 112 , first paragraph, rejection grounded on 'lack of utility' basis unless a 35 U.S.C. § 101 rejection is proper." M.P.E.P. § 2107(IV) at 2100-36. Since the claimed invention complies with the utility requirement of 35 U.S.C. § 101, the rejection of claims 21, 26, 33, and 35-37 under 35 U.S.C. § 112, first paragraph, based on lack of utility of the claimed invention, should be withdrawn.

VII. Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 34 and 37 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. *See*, Paper No.17, page 6, first paragraph. In particular, the Examiner states at page 6, third paragraph of the Office Action that "it is unclear if 'the protein' recovered is said isolated protein of claim 21 or if it is another protein in/from the cell."

Applicants respectfully disagree, but solely in the interest of facilitating prosecution, Applicants have amended claim 37, thereby obviating the rejection. Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claim 37 under 35 U.S.C. § 112, second paragraph.

In addition, the Examiner has indicated that claim 34 is indefinite for allegedly failing to indicate the relationship between the recited structural elements. Specifically, the Examiner states at page 6, fourth paragraph of the Office Action:

> it is not clear how the 'heterologous polynucleotide' of claim 34, for example, relates to the polynucleotide of claim 21. In claim 34, it is not clear whether the heterologous sequence is attached at the end or might be internally inserted.

Applicants respectfully disagree.

Preliminarily, Applicants point out that claim 34 recites "heterologous polypeptide" not "heterologous polynucleotide," as stated by the Examiner. In addition, claim 21 recites "polypeptide" not "polynucleotide," as stated by Examiner.

According to M.P.E.P. § 2173.02:

> Definiteness of claim language must be analyzed, not in a vacuum, but in light of:
> (A) The content of the particular application disclosure;
> (B) The teachings of the prior art; and
> (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. M.P.E.P. § 2173.02 at 2100-194.

Applicants respectfully point out that claim 34, interpreted by one skilled in the art, in view of the teachings of the specification, clearly indicates the relationship between the recited structural elements. Nonetheless, solely in the interest of facilitating prosecution, Applicants have amended claim 34, thereby obviating the rejection. Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claim 34 under 35 U.S.C. § 112, second paragraph.

Conclusion

Applicants respectfully request that the above-made remarks be entered and made of record in the file history of the instant application. If there are any fees due in connection with the filing of this paper, please charge the fees to our Deposit Account No. 08-3425. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

Dated: March 26, 2002

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THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Meissner et al.

Application Number: 09/393,023 Group Art Unit: 1646

Filed: September 9, 1999 Examiner: Kaufman, C.

Title: Human Criptin Growth Factor Attny. Docket No.: PF200D1

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims

Please amend the claims as follows:

34. (Once Amended) The isolated protein of claim 24, wherein the amino acid sequence [further comprises] is fused to a heterologous polypeptide.

37. (Once Amended) A protein produced by a method comprising:

(a) culturing a host cell under conditions suitable to produce the isolated protein of claim 21; and

(b) recovering [the] said protein produced by the method.